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Waldenström's Macroglobulinemia Resulting From Localized Gastric Lymphoplasmacytoid Lymphoma

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A patient with a high level serum monoclonal IgM lambda paraprotein (3,850 mg/dL) was found to have a mass infiltrating the gastric mucosa. Gastric biopsy with immunohistochemical stains showed a B-cell lymphoplasmacytoid infiltrate expressing IgM lambda, consistent with Waldenström's macroglobulinemia. The patient's response to gastric radiation indicated that the primary source of the macroglobulinemia was the stomach. This is an extremely rare presentation, with only six other reported cases of this entity with gastric involvement. Am. J. Hematol. 58:244–245, 1998. © 1998 Wiley-Liss, Inc.

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CASE REPORT

A 61-year-old white female with no significant past medical history was referred for evaluation of hypergammaglobulinemia. She had complaints of intermittent paresthesias in her fingers and toes for 6 months. She admitted to frequent headaches, but denied any visual changes, easy bleeding, bruising, epistaxis, Raynaud's symptoms, change in appetite, or melena.

Her physical exam was significant for a 10-cm mass palpable in the left upper quadrant with mild epigastric tenderness. The remainder of the exam was within normal limits, including a normal fundoscopy and neurological exam.

Significant laboratory findings included a normal CBC and differential, with occasional rouleaux formation noted on peripheral blood smear. Serum protein electrophoresis showed elevated total protein measuring 9.3 g/dL and elevated gammaglobulins measuring 2.7 g/dL with a monoclonal band in the gamma region identified as IgM lambda by immunofixation. Serum IgM measured 2,990 mg/dL by nephelometry (normal 63–277 mg/dL). IgM quantitation performed 2 weeks earlier by another lab measured 3,850 mg/dL. Plasma viscosity was 2.9 centipoises (normal 1–2). Anti-myelin-associated glycoprotein (MAG) antibody was negative.

A CT scan of the abdomen was performed to evaluate the palpable mass and revealed a diffusely thickened gastric wall. There was no mesenteric or retroperitoneal lymph node enlargement and liver and spleen sizes were normal. Gastric biopsies taken during endoscopy revealed an atypical lymphoid cell infiltrate consistent with lymphoplasmacytoid lymphoma (immunocytoma). Immunohistochemical stains showed a dense B-cell infiltrate expressing IgM and lambda. Stains for *Helicobacter pylori* and a CLO test were both negative.

The bone marrow biopsy revealed a single lymphoid aggregate without significant lymphocytic infiltration in the interstitial tissue. Marrow aspirate smears suggested a slight increase in the number of lymphocytes, plasmacytoid lymphocytes, and plasma cells. Pan-T- and pan-B-cell immunostains performed on the bone marrow aspirate were unremarkable. Flow cytometry of the marrow aspirate revealed only 1% of the lymphocytes were B cells. Thus there was no definite evidence of lymphoplasmacytoid lymphoma involving the bone marrow.

Based on the immunohistochemistry of the gastric biopsy, the patient was diagnosed with Waldenström's macroglobulinemia and treated with intravenous cyclo-

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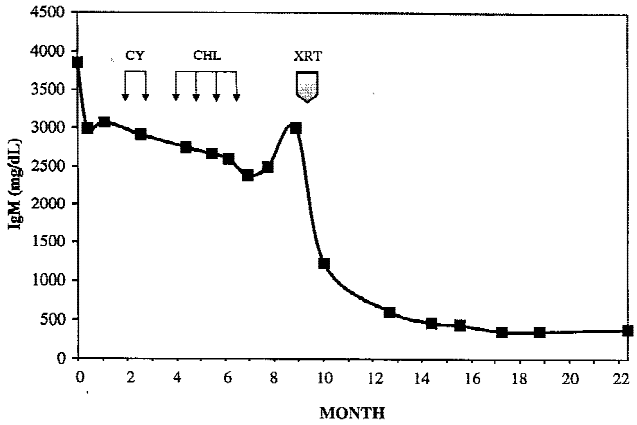

Fig. 1. IgM levels in response to therapy. CY: IV cyclophosphamide 750 mg/m^2 with prednisone 40 mg/m^2; CHL: oral chlorambucil 0.9 mg/kg with prednisone 40 mg/m^2; XRT: 32 Gray of conformal radiotherapy in 23 fractions.

phosphamide and prednisone. The patient developed life-threatening SIADH after the second cycle of cyclophosphamide and the treatment was changed to chlorambucil. Following four monthly cycles of chlorambucil and prednisone, a CT scan of the abdomen showed no change in gastric wall thickness and the IgM level measured 2,370 mg/dL (Fig. 1). Chemotherapy was discontinued and the patient received a total dose of 32 Gray of fractionated conformal radiotherapy targeted exclusively to the stomach. Ten days following the completion of radiotherapy, the patient's IgM level had decreased to 1,230 mg/dL. A CT scan performed 2 months later showed a 1-cm reduction in gastric wall thickening. Three months following radiotherapy, the IgM level had decreased to 613 mg/dL with a faint monoclonal band in the gamma region on SPEP. Her neurologic symptoms and headaches disappeared, and her IgM level progressively decreased over the next 8 months to 384 mg/dL (Fig. 1). Mild thickening of the gastric wall persists on CT scan 14 months following radiotherapy, but remains unchanged from the initial post-radiotherapy scan.

DISCUSSION

Jan Waldenström initially described a syndrome of hypergammaglobulinemia of IgM, elevated viscosity and ESR, anemia, and bleeding tendency caused by a macroglobulinemia secondary to bone marrow infiltration of plasmacytoid lymphocytes and overproduction of monoclonal antibody [1]. These patients are usually older males, 20–40% of whom have lymphadenopathy and/or splenomegaly. The clinical presentation reflects both the effects of the paraprotein, such as hyperviscosity syndrome, cryoglobulinemia, anemia, neuropathy, glomerular disease, and/or concurrent amyloidosis, as well as the effects of tumor infiltration, which generally involves bone marrow, lymph nodes, and/or spleen [2]. Neurologic deficits are common in patients with Waldenström's macroglobulinemia, with approximately 33% of patients developing a peripheral sensory neuropathy. They typically present with progressive distal paresthesias or pain. Only half of these patients are positive for anti-MAG reactivity [3].

Review of the literature revealed only six other cases of Waldenström's macroglobulinemia occurring in the gastric mucosa. One patient with epigastric pain and melena was found to have a lymphoplasmacytoid infiltrate on gastric biopsy with a normal bone marrow [4]. The other five reported cases with gastric localization are in the French [5,6], Japanese [7], Polish [8], and Italian literature [9]. It is unclear whether these patients had bone marrow involvement as well as gastric infiltrates.

Our patient presented with paresthesias as the only symptom and was found to have a high level serum monoclonal IgM paraprotein and gastric lymphoplasmacytoid lymphoma. Immunohistochemical stains of the gastric biopsy suggested that the source of the macroglobulinemia was the gastric mucosal lymphoma. Confirmation of this occurred after gastric radiation therapy, which simultaneously decreased the gastric wall thickness by CT scan and the serum IgM level. If lymphoplasmacytic infiltrates at other sites, such as the bone marrow, had been contributing significantly to the macroglobulinemia, then the IgM level should not have responded so well to gastric radiotherapy. Thus, we present a case of Waldenström's macroglobulinemia due to localized gastric lymphoplasmacytoid lymphoma without detectable involvement at typical disease sites.

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